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(71) Applicant: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors: KRISTIANSON, J., Krister ; Olofsgatan 13, S-193 00 Sigtuna (SE). WOLDOLSEN, Per ; 454-191 Prospect Avenue, West Orange, NJ 07052 (US).

(74) Agent: NICHOLSON, William, H.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: COMBINATIONS OF ACE INHIBITORS AND DIURETICS

(57) Abstract

Pharmaceutical formulations comprising as active ingredients an angiotensin converting enzyme (ACE) inhibitor at a dose level normally found effective as an antihypertensive and a diuretic at a dose level below its minimum effective dose, demonstrate greater efficacy than would be expected in returning the blood pressure of hypertensive patients to normotensive values.

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TITLE OF THE INVENTION

COMBINATIONS OF ACE INHIBITORS AND DIURETICS

BACKGROUND OF THE INVENTION

Both diuretics and ACE-inhibitors have an effect on the renin-angiotensin-aldosterone system. ACE-inhibitors act by inhibiting the conversion of angiotensin I to angiotensin II. Diuretics regulate the sodium-balance, and thereby also fluid volume. The decrease, both in sodium as well as volume, following therapy with diuretics increases plasma renin activity and thereby activates the renin-angiotensin-aldosterone system. This effect will to some degree counteract the blood-pressure lowering effect of the diuretic. When a diuretic and an ACE-inhibitor are combined the different pharmacological actions of these two drugs will,

influence the effect of the other. There is accordingly a logical rationale for combining these two pharmacological principles.

It is possible to establish the highest non-pharmacological active dose of diuretic, i.e. a dose that is so low that it has no effect on blood pressure, and no apparent adverse effects. The highest non-effective dose of diuretic will still trigger the renin-angiotensin-aldosterone system and although it has no physiological effect of it's own, it will nonetheless have a potentiating effect on an ACE-inhibitor.

In a recently completed study by us of the effects of different doses of HCTZ on blood pressure and various metabolic parameters, doses ranging from 3 mg to 25 mg were investigated. 25 mg HCTZ produced significant effects on blood pressure and the metabolic parameters. 12.5 mg of HCTZ was found to be at the threshold of an effective antihypertensive response, and changes were seen in the metabolic parameters. Contrary to this, the doses of 3 and 6 mg were demonstrated not to be different from placebo in effects on blood pressure and various metabolic parameters.

Based on this study it can be concluded that 6 mg has been established as the highest non-pharmacological dose of HCTZ.

In a study by Andren et al., J. Hypertension 1 (suppl. 2) 384-386 (1983)) doses of 6.25, 12.5 and 25 mg of hydrochlorothiazide (HCTZ) were combined with 10 and 40 mg of enalapril respectively. The authors concluded that: "the five combinations were equally effective in reducing blood pressure, and when given with enalapril the dose of HCTZ can be very low". When the Andren study was performed, it

was not known by him that 6.25 mg is or is close to the non-pharmacological dose.

SUMMARY OF THE INVENTION

This invention is concerned with pharmaceutical formulations for the treatment of essential hypertension and disorders associated therewith such as congestive heart failure which have as active ingredients an angiotensin converting enzyme (ACE) inhibitor and a diuretic wherein the diuretic is at a dose level below the recognized pharmacological dose.

With these formulations the ACE inhibitor is found to have greater efficacy in reducing elevated blood pressure to normal levels than it would have if used at the same dose in monotherapy. At the same time the diuretic is being administered at dose levels that would be ineffective as an antihypertensive if used alone and similarly ineffective in causing adverse reactions.

DETAILED DESCRIPTION OF THE INVENTION

The novel pharmaceutical formulations of this invention comprise: a pharmaceutical carrier; an ACE inhibitor at the dose level normally employed in monotherapy, which is usually about 5-50 mg, depending on the ACE inhibitor; and a diuretic at a dose level which is the highest non-pharmacological dose.

The formulation is designed for oral administration and is presented as tablets, capsules, gel caps, caplets or as a sustained release formulation. It may also be designed as an elixir

for oral administration, or a suppository for rectal administration.

Illustrative of the excipients which can be incorporated in tablets, capsules and the like are: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

The novel formulations of this invention are useful in the treatment of essential hypertension, and congestive heart failure.

The ACE inhibitors useful in the novel formulation and method of treatment of this invention are enalapril, lisinopril, captopril alacipril, benazapril, cilazapril, delapril, fosinopril, perindopril, quinapril, ramipril, moveltipril, spirapril, ceronapril, imidapril, temocapril, trandolopril, utilbapril, zofenopril, CV5975, EMD-56855, libenzapril, zalicipril, HOE065, MDL 27088, AB47, DU 1777, MDL 27467A, Equaten™, Prenty1™, Synecor™, and Y23785.

Preferred ACE inhibitors are enalapril, lisinopril, captopril, perindopril, benzapril, quinapril, and cilazapril, especially enalapril.

The diuretics useful in the novel formulation and method of treatment of this invention are: hydrochlorothiazide (HCTZ), furosemide, altizide, trichlormethazide, triflumethazide, bemetizide, cyclothiazide, methylchlothiazide, azosemide, chlorothiazide, butizide, bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide, hydroflumethazide, benzthiazide, ethiazide, penflutazide.

Preferred diuretics for incorporation in the novel formulation of this invention are hydrochlorothiazide, trichlormethazide, furosemide and altizide, especially hydrochlorothiazide.

In the specification and claims hereof, the naming of an ACE inhibitor or diuretic such as enalapril or hydrochlorothiazide respectfully is meant to include salts thereof such as enalapril maleate.

The novel method of treatment of this invention comprises the administration of a unit dose of the novel pharmaceutical formulation, one to three

times a day depending on the patient and the severity of the indication being treated. Usually once or twice a day is adequate.

EXAMPLE 1

Component	Amount (mg)		
	A	B	C
enalapril maleate	20	10	5
hydrochlorothiazide	6	6	6
sodium bicarbonate	10	5	2.5
lactose	154	164.1	198.1
starch NF	22	22	22.77
pregelatinized starch NF	2.2	2.2	5.06
magnesium stearate	1.1	1.0	0.90

The excipients shown in Example 1 are exemplary of the substituents used in each of the other examples that follow.

EXAMPLE 2

Component	Amount (mg)		
	1	2	3
lisinopril	20	10	5
hydrochlorothiazide	6	6	6

EXAMPLE 3

Component	Amount (mg)		
	1	2	3
Captopril	50	25	12.5
hydrochlorothiazide	6	6	6

EXAMPLE 4

Component	Amount (mg)		
	1	2	3
Benazapril	40	20	10
hydrochlorothiazide	6	6	6

EXAMPLE 5

Component	Amount (mg)		
	1	2	3
Quinapril	20	10	5
hydrochlorothiazide	6	6	6

EXAMPLE 6

Component	Amount (mg)		
	1	2	3
Cilazapril	50	25	12.5
hydrochlorothiazide	6	6	6

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising a pharmaceutical carrier; about 5-50 mg of an angiotensin converting enzyme inhibitor; and a non-pharmacological dose of a diuretic.

2. The pharmaceutical formulation of Claim 1, wherein the angiotensin converting enzyme inhibitor is selected from enalapril, lisinopril, captopril alacipril, benazapril, cilazapril, delapril, fosinopril, perindopril, quinapril, ramipril, moveltipril, spirapril, ceronapril, imidapril, temocapril, trandolopril, utilbapril, zofenopril, CV5975, EMD 56855, libenzapril, zalicipril, HOE065, MDL 27088, AB47, DU 1777, MDL 27467A, Equaten™, Prentyl™, Synecor™, and Y23785; and the diuretic is selected from hydrochlorothiazide (HCTZ), furosemide, altizide, trichlormethazide, triflumethazide, bemetizide, cyclothiazide, methylchlothiazide, azosemide, chlorothiazide, butizide, bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide, hydroflumethazide, benzthiazide, ethiazide, penflutazide.

3. The formulation of Claim 2, wherein the angiotensin converting enzyme inhibitor is selected from enalapril, lisinopril, captopril, perindopril, benazapril, quinapril, and cilazapril; and the diuretic is selected from hydrochlorothiazide, trichlormethazide, furosemide and altizide.

4. The formulation of Claim 3, wherein the angiotensin converting enzyme inhibitor is enalapril, and the diuretic is hydrochlorothiazide.

5. The formulation of Claim 4 comprising 5, 10 or 20 mg of enalapril and 6 mg of hydrochlorothiazide.

6. A method of treating hypertension and congestive heart failure, which comprises the administration to a patient in need of such treatment of a pharmaceutical formulation comprising a pharmaceutical carrier; about 5-50 mg of an angiotensin converting enzyme inhibitor; and a non-pharmacological dose of a diuretic.

7. The method of Claim 6, wherein the angiotensin converting enzyme inhibitor is selected from enalapril, lisinopril, captopril alacipril, benazapril, cilazapril, delapril, fosinopril, perindopril, quinapril, ramipril, moveltipril, spirapril, ceronapril, imidapril, temocapril, trandolopril, utilbapril, zofenopril, CV5975, EMD 56855, libenzapril, zalicipril, HOE065, MDL 27088, AB47, DU 1777, MDL 27467A, Equaten™, Prentyl™, Synecor™, and Y23785; and the diuretic is selected from hydrochlorothiazide (HCTZ), furosemide, altizide, trichlormethazide, triflumethazide, bemetizide, cyclothiazide, methylchlothiazide, azosemide, chlorothiazide, butizide, bendroflumethazide, cyclopenthiazide, benzclortriazide, polythiazide, hydroflumethazide, benzthiazide, ethiazide, penflutazide.

8. The method of Claim 7 wherein the angiotensin converting enzyme inhibitor is selected from enalapril, lisinopril, captopril perindopril, benazapril, quinapril, and cilazapril; and the diuretic is selected from hydrochlorothiazide, taichlormethazide, furosemide and altizide.

9. The method of Claim 8 wherein the angiotension converting enzyme inhibitor is enalapril and the diuretic is hydrochlorothiazide.

10. The method of Claim 9 comprising 5, 10 or 20 mg of enalapril and 6 mg of hydrochlorothiazide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01813

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/54,31/40,
US CL :514/223.5,423 .
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS and Cas Online:ACE inhibitors, diuretic, hypertension, heart, cardio?, enalapril, hydrochlorothiazide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Journal of Hypertension, 1983, Andren et al., Enalapril with either a 'verylow' or 'low' dose of hydrochlorothiazide is equally effective in essential hpertension, pages 384-386.	1-10
Y	Chemical Abstract, volume 111, no. 9, Becker et al.; "Loop dinnetics combined with an ACE inhibjtor for treatment of hypertension: a study with furosemide, piretanide, and ramipil in spontaneously hypertensive rats", abstract no. 70668h, J. Cardiovasc. Pharma col., 1989, 13 (Suppl. 3), p. 535-539.	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Authorized officer
KIMBERLY JORDAN

Telephone No. (703) 308-1235

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